

Table S1: CDD families with multi-binding interfaces and interaction partners. The first column gives domain family name and its corresponding cluster-id number.

Domain super Family	Interacting domain partners		Interacting chains		Interface overlap ratio
	Partner1	Partner2	PDB1	PDB2	
558, Ubiquitin					
	Ubiquitin-conjugating enzyme E2, smart00212	Ubiquitin Associated domain, pfam00627	1ZGU:B-A	3G3Q:B-A	55
	Ubiquitin-conjugating enzyme E2, smart00212	A20-like zinc fingers; smart00259	1ZGU:B-A	2C7N:D-C	79
	ThiF_MoeB_HesA. Family of E1-like enzymes, cd01483	Ubiquitin Associated domain, pfam00627.	1JWB:D-B	2G3Q:B-A	54
	ThiF_MoeB_HesA. Family of E1-like enzymes, cd01483	Peptidase_C12, pfam01088	1JWB:D-B	1CMX:B-A	53
	ThiF_MoeB_HesA. Family of E1-like enzymes, cd01483	MoaE family, pfam02391	1JWB:D-B	1FMA:D-E	52
	ThiF_MoeB_HesA. Family of E1-like enzymes, cd01483	Peptidase_C48_Ulp1 protease family, pfam02902	1JWB:D-B	1XT9:B-A	55
	ThiF_MoeB_HesA. Family of E1-like enzymes, cd01483	GAT domain, pfam03127	1JWB:D-B	1WR6:G-C	58
	Uracil DNA glycosylase superfamily, pfam03167	Skp1 protein family, smart00512	1WYW:B-A	1LQB:A-B	50
	Ubiquitin Associated domain, pfam00627.	Peptidase_C12, pfam01088	2G3Q:B-A	1CMX:B-A	53

	Ubiquitin Associated domain, pfam00627.	Repeat in ubiquitin-activating (UBA), pfam02134	2G3Q:B-A	1R4N:K-F	59
	Ubiquitin Associated domain, pfam00627.	MoaE family, pfam02391	2G3Q:B-A	1JWB:D-E	52
	Ubiquitin Associated domain, pfam00627.	GAT domain, pfam03127	2G3Q:B-A	1WR6:G-C	73
	Ubiquitin Associated domain, pfam00627.	A20-like zinc fingers; smart00259	2G3Q:B-A	2C7N:D-C	73
	Repeat in ubiquitin-activating (UBA), pfam02134	Peptidase_C12_pfam01088	1R4N:K-F	1CMX:B-A	52
	GAT domain, pfam03127	A20-like zinc fingers; smart00259	1WR6:G-C	2C7N:D-C	59
<i>1936, Immunoglobulin</i>					
	Voltage gated chloride channel, pfam00654	C-type lysozyme, cd00119	1OTS:E-B	1FBI:Q-Y	60
	Voltage gated chloride channel, pfam00654	Sialidases or neuraminidases , cd00260	1OTS:E-B	1A14:H-N	58
	Voltage gated chloride channel, pfam00654	Class II histocompatibility antigen, beta domain, pfam00969	1OTS:E-B	1YMM:D-B	50
	C-type lysozyme, cd00119	Sialidases or neuraminidases , cd00260	1J1P:L-Y	2AEP:L-A	58
	C-type lysozyme, cd00119	Rieske domain, cd03467	1T6V:N-L	1KYO:J-E	53
	C-type lysozyme, cd00119	Class II histocompatibility antigen, beta domain, pfam00969	1VFB:B-C	1YMM:D-B	64
	C-type lysozyme, cd00119	von Willebrand factor type A domain, pfam00092	1P2C:E-F	1MHP:X-B	59
	C-type lysozyme, cd00119	Class I Histocompatibility antigen, pfam00129	1JTO:A-L	2F53:E-A	60

	Sialidases or neuraminidases , cd00260	Cytochrome C oxidase subunit II, pfam00116	2AEP:L-A	1AR1:D-B	56
	Cytochrome C oxidase subunit II, pfam00116	Rieske domain, cd03467	1AR1:C-B	1KYO:J-E	54
	Class I Histocompatibility antigen, pfam00129	Class II histocompatibility antigen, beta domain, pfam00969	1MO5:B-C	1D9K:F-H	50
	Class I Histocompatibility antigen, pfam00129	Staphylococcal/Streptococcal toxin, pfam01123	2F53:E-A	1JCK:A-B	50
	Class I Histocompatibility antigen, pfam00129	von Willebrand factor type A domain, pfam00092	1MI5:D-A	1MHP:X-B	50
<i>1990 Trypsin-like Serine protease</i>					
	BPTI/Kunitz family of serine protease inhibitors, cd00109	Kazal type serine protease inhibitors ,smart00280	1BTH:K-Q	1TBR:H-R	61
	BPTI/Kunitz family of serine protease inhibitors, cd00109	Antithrombin-III like, cd023045	1BTH:K-Q	1TB6:H-I	58
	BPTI/Kunitz family of serine protease inhibitors, cd00109	Soybean trypsin inhibitor (Kunitz) family of protease inhibitors, cd00178	1BTH:K-Q	1AVW:A-B	53
	BPTI/Kunitz family of serine protease inhibitors, cd00109	Protease Inhibitor Ecotin, cd00242	1BTH:K-Q	1XX9:B-D	56
	Kazal type serine protease inhibitors ,smart00280	Antithrombin-III like, cd023045	TBR:H-R	1TB6:H-I	70
	Kazal type serine protease inhibitors ,smart00280	Protease Inhibitor Ecotin, cd00242	TBR:H-R	1XX9:B-D	55
	Antithrombin-III like, cd023045	Soybean trypsin inhibitor (Kunitz) family of protease inhibitors, cd00178	1TB6:H-I	1AVW:A-B	64

	Antithrombin-III like, cd023045	Protease Inhibitor Ecotin, cd00242	1TB6:H-I	1XX9:B-D	67
	Soybean trypsin inhibitor (Kunitz) family of protease inhibitors, cd00178	Protease Inhibitor Ecotin, cd00242	1AVW:A-B	1XX9:B-D	68
<i>17 Small GTPases</i>					
	GDP dissociation inhibitor, pfam00996	Dbs pleckstrin homology (PH) domain, cd01227	1UKV:Y-G	1LB1:H-G	50
	GDP dissociation inhibitor, pfam00996	RHO protein GDP dissociation inhibitor, pfam02115	1UKV:Y-G	1HH4:A-D	53
	Importin-beta N- terminal domain, pfam03810	Dbs pleckstrin homology (PH) domain, cd01227	2BKU:C-D	1LB1:H-G	50
	Importin-beta N- terminal domain, pfam03810	RHO protein GDP dissociation inhibitor, pfam02115	2BKU:C-D	1HH4:A-D	53
	Rab family, cd00154	Guanine nucleotide exchange factor for Ras-like small GTPases, cd00155	1T91:C-D	1NVX:Q-S	50
	Arfaptin domain, cd00011	Guanine nucleotide exchange factor for Rho/Rac/Cdc42- like GTPases, cd00160	1I4T:D-A	1X86:F-E	67
	Arfaptin domain, cd00011	Heat-labile enterotoxin alpha chain, pfam01375	1I4T:D-A	2A5D:A-B	56
	Guanine nucleotide exchange factor for Rho/Rac/Cdc42-like GTPases, cd00160	Heat-labile enterotoxin alpha chain, pfam01375	1X86:F-E	2A5D:A-B	50
	GRIP domain, pfam01465	WD40 repeats, smart00320	1UPT:A-B	1GOT:A-B	50
<i>2110, peptidase_S8</i>					
	Potato inhibitor I family, pfam00280	KAZAL_PSTI, cd01327	1MEE:A-I	1YU6:A-C	85

	Potato inhibitor I family, pfam00280	Subtilisin N-terminal, pfam05922	1MEE:A-I	1SPB:S-P	53
	KAZAL_PSTI, cd01327	Subtilisin N-terminal, pfam05922	1YU6:A-C	1SPB:S-P	52
5305, WD40					
	Beta adrenergic receptor kinase, cd01240	G protein alpha subunit, cd00066	2BCJ:B-A	1GG2:B-A	50
	Beta adrenergic receptor kinase, cd01240	Phosducin, pfam02114	2BCJ:B-A	1AOR:B-P	62
	G protein alpha subunit, cd00066	Phosducin, pfam02114	1GG2:B-A	1AOR:B-P	50
2393, FAD Binding					
	2Fe-2S iron-sulfur cluster binding domain, cd00207	2Fe-2S binding domain, pfam01799	1T3Q:C-A	1N62:F-D	64
3072, Beta-Ketoacyl synthase					
	Beta-ketoacyl synthase, pfam00109	Thiolase, N-terminal domain, pfam00108	1E5M:A-A	2C7Y:A-A	55
2129, Class I Histocompatibility antigen					
	carbohydrate-recognition domain (CRD), smart00034	Immunoglobulin, smart00409	1HYR:C-B	1MI5:A-D	50
	Immunoglobulin domain variable region (v), cd00099	Class I Histocompatibility antigen, pfam00129	3F53:A-E	1A6Z:C-A	52
57, Ribosomal protein S14p/S29e					
	K homology RNA-binding domain, type II, cd02409	Ribosomal protein S3, N-terminal domain. pfam00417	1PNS:N-C	1HR0:N-C	90

<i>539, Histidine-containing phosphocarrier protein (HPr)-like protein</i>					
	Periplasmic binding proteins, pfam00532	PEP-utilising enzyme, N-terminal. Pfam05524	1RZR:Y-D	3EZA:B-A	64
<i>1128, Plastocyanin</i>					
	Apocytochrome F, C-terminal. pfam01333	Methylamine dehydrogenase heavy chain (MADH), pfam06433	2PCF:A-B	1MG2:O-M	57
<i>1191, Thiamine pyrophosphate (TPP) enzyme</i>					
	Transketolase, pyrimidine binding domain, pfam02779	Thiamine pyrophosphate enzyme, pfam02776	2BP7:G-H	1PYD:B-B	54
<i>1939</i> <i>Immunoglobulin like fold</i>					
	Alpha amylase, catalytic domain, pfam00128	Glycosyl hydrolase family 9, pfam00759	1DED:B-B	1RQ5:A-A	64
<i>1941</i> <i>Kazal type serine protease inhibitors</i>					
	Trypsin-like serine protease, cd00190	Subtilase family, pfam00082	1TBR:R-H	1YU6:C-A	53
<i>2093</i> <i>Transforming growth factor beta like domain</i>					
	Kazal type serine protease inhibitors, smart00280	Activin types I and II receptor domain, pfam01064	2ARP:A-F	1S4Y:B-A	56

2173					
	<i>Carbamoyl-phosphate synthase L chain, N-terminal</i>				
	Methylglyoxal synthase-like domain (MGS_CPS_II), cd01424	Carbamoyl-phosphate synthetase large chain, oligomerisation domain, pfam02787	1T36:C-C	1CSO:A-A	52
2258					
	<i>RNA polymerase Rpb2</i>				
	RNA polymerase Rpb3/RpoA insert domain, pfam01000	DNA-directed RNA polymerase, subunit L, COG1761	1I6V:C-B	1I3Q:B-K	50
3096					
	<i>Pyridine nucleotide-disulphide oxidoreductase</i>				
	UDP-galactopyranose mutase, COG0562	Ribulose 1,5-bisphosphate synthetase, COG1635	1JEH:A	2F5Z:B	55
3110					
	<i>Streptococcal toxin, beta-grasp domain</i>				
	Immunoglobulin domain constant region, cd00098	Staphylococcal/Streptococcal toxin, pfam01123	1D6E:C-A	1B1Z:B-A	50
4102					
	<i>RNA polymerase Rpb1</i>				
	RNA polymerase Rpb2, domain 6, pfam00562	RNA polymerase Rpb1, domain 4, pfam05000	1R9T:A-B	2GHO:D-D	50

<i>4111</i>					
<i>RNA poly Rpb1 dom 4</i>					
	RNA polymerase beta subunit, pfam04563	RNA polymerase Rpb2, domain, pfam04567	1R9T:A-B	1R9T:A-B	50
<i>1648 PH-like</i>					
	Dynamin pleckstrin homology (PH) domain, cd01256	Regulator of G protein signalling domain, smart00315	1DYN:A-B	2BCJ:A-A	64
	PH_cytohesin, cd01252	WD40 repeats, smart00320	1FHX:B-A	2BCJ:A-B	60
<i>1309, Rnase</i>					
	RNase_Sa, cd00607	Barstar (barnase inhibitor), pfam01337	1PYL:A-B	1X1U:B-E	72
<i>1981, SH3</i>					
	SH2, cd00173	SH3, smart00326	1X27:A-E	1VA7:D-A	57
<i>2109, Sod_Fe_N</i>					
	Sod_Fe_N, pfam00081	Sod_Fe_C, pfam02777	1B06:C-F	2GDS:D-A	50
<i>2254, Integrase DNA binding domain</i>					
	Integrase core domain, pfam00665	Integrase DNA binding domain, pfam00552	1COM:C-C	1C1A:B-A	77
<i>2263, Transthyretin</i>					
	Transthyretin, smart00095	Lipocalin, pfam00061	1ICT:A-F	1QAB:A-E	75
<i>2414, RNA_pol_A_bac</i>					

	RNA polymerase Rpb3/RpoA insert domain, pfam01000	DNA-directed RNA polymerase, subunit L, COG1761	1ZYR:K-L	1YIV:C-K	50
88, <i>GST_N_family</i>					
	GST_C_EFB1gamma, cd03181	PDI_b_Calsequestrin_N, cd03065	1G6W:C-B	1SJI:A-A	56
95, <i>AdoHcyase_NAD</i>					
	NAD(P) transhydrogenase beta subunit, pfam02233	Alanine dehydrogenase/PNT, C-terminal domain, pfam01262	1FR8:A-C	1L7E:B-C	57
174, <i>fer2</i>					
	FAD_binding_5, pfam00941	fer2, cd00207	1T3Q:A-C	1XLP:C-A	56
177, <i>HTH_ARSR</i>					
	Iron dependent repressor, pfam02742	helix_turn_helix ASNC type, smart00344	1BI2:A-A	2CFX:G-D	50
256, <i>globin</i>					
	Oxidoreductase FAD-binding domain, pfam00970	Globin, cd01040	1GVH:A-A	1UC3:F-H	52
450, <i>Serine/Threonine protein kinases</i>					
	Serine/Threonine protein kinases, cd00180	Regulator of G protein signalling domain, smart00315	1ZYC:A-C	2BCJ:A-A	50
646, <i>Histidine Phosphotransfer domain</i>					
	Signal receiver domain, cd00156	Histidine Phosphotransfer domain, smart00073	10XB:A-B	1C03:C-A	64
1808, <i>Zinc-dependent</i>					

<i>metalloprotease</i>					
	Tissue inhibitor of metalloproteinase, smart00206	Zinc-dependent metalloprotease, cd00203	1OO9:A-B	1OS2:C-B	51
<i>1946, BPTI/Kunitz family of serine protease inhibitors</i>					
	BPTI/Kunitz family of serine protease inhibitors, cd00109	Trypsin-like serine protease, cd00190	2HEX:C-D	1CAO:I-G	53
<i>1964, PDGF</i>					
	Immunoglobulin, smart00409	Platelet-derived and vascular endothelial growth factors (PDGF), cd00135	1RV6:W-X	2GNN:A-D	70
<i>1979, SERPIN</i>					
	Antithrombin-III like, cd02045	Trypsin-like serine protease, cd00190	1LK6:I-L	1TB6:I-H	70
<i>1980, SH2</i>					
	Protein Tyrosine Kinase (PTKc), cd00192	SH2, cd00173	1OPL:A-A	1R1S:G-A	50
<i>2095, Actin</i>					
	Profilin (PROF), smart00392	Actin, pfam00022	1HLU:A-P	1LCU:A-B	52
<i>2100, EF hand</i>					
	Myosin MYSc, smart00242	EF hand, pfam00036	2BKH:B-A	1K2H:A-B	50
<i>2274, GEL</i>					
	Gelsolin homology domain (GEL), smart00262	Actin, pfam00022	2FGH:A-A	1P8Z:G-A	55
<i>2287,</i>					

<i>Ricin_B_lectin</i>					
	Glycosyl hydrolase family 10, smart00633	Ricin-type beta-trefoil lectin domain, pfam00652	1V6W:A-A	1ISV:B-A	67
<i>2314, DNA_pol3_beta_2</i>					
	DNA polymerase III beta subunit central domain, pfam02767	DNA polymerase III beta subunit, C-terminal domain, pfam02768	1VPK:A-A	1MMI:B-B	52
<i>2838, B1</i>					
	Immunoglobulin, smart00409	Protein L b1 domain, pfam02246	1HEZ:E-C	1XF5:M-L	72
<i>3051, Acyl-CoA_dh_N</i>					
	Acyl-CoA dehydrogenase, C-terminal, pfam00441	Acyl-CoA dehydrogenase, N-terminal, pfam02771	1BUC:A-B	1WS9:A-B	50
<i>3592, Malic_M</i>					
	Malic enzyme, N-terminal, pfam00390	Malic enzyme, NAD binding, pfam03949	1PJ2:C-B	1PJ3:C-B	50